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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/211,297	12/14/1998	WILLIAM J. BOYLE	A-451-F	7253

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AMGEN INC.
MAIL STOP 28-2-C
ONE AMGEN CENTER DRIVE
THOUSAND OAKS, CA 91320-1799

EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/211,297	BOYLE, WILLIAM J.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *82-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response received January 25, 208 is acknowledged.

Claims 82-92 are pending in the instant application.

Information Disclosure Statement

2. Applicants IDS form received August 14, 2007 is acknowledged and has been considered.

Claim Rejections - 35 USC § 102/103

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 82-92 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Gorman et al. (US Patent No. 6,242,586, of record as reference B on form 892 dated March 27, 2003, see entire document).

Gorman et al. disclose antibodies which bind a TNF ligand family member identified as 499E9 (see entire document, particularly the abstract). The mouse sequence of 499E9 is disclosed and this polypeptide is mouse OPGbp. Gorman et al. further disclose that human and other species homologs of 499E9 are other embodiments of their invention (see particularly lines 44-50 of column 9 and Example 4). The antibodies disclosed by Gorman et al. are characterized as being neutralizing and blocking antibodies, and that such antibodies can be made in a variety of hosts, including humans (see particularly lines 55-58 of column 12, lines 65-67 of column 15, the paragraph spanning columns 20 and 21, and lines 52-54 of column 21). Such antibodies are further disclosed as being present in pharmaceutical compositions for use in the treatment of various diseases and conditions (see particularly columns 20 and 21). Antibody compositions are disclosed as comprising additional ingredients such as carriers, adjuvants, and other biologically active compounds (see particularly columns 21 and 22).

The instant specification discloses that OPGL blocking antibodies inhibit osteoclast formation by binding the BB' and EF loops of OPGbp and thus blocking the interaction of OPGbp with OPG. Given that OPGbp and 499E9 are the same protein, it appears that the blocking antibodies disclosed by Gorman et al. must bind the recited epitopes because they are blocking antibodies, and blocking antibodies bind the BB' and EF loops of OPGbp/499E9. Alternatively, given that the antibodies of Gorman et al. are blocking antibodies, and that there is a finite, limited number of epitopes which when bound by an antibody confer blocking ability as is disclosed in the instant specification, it also appears reasonable that a blocking antibody would bind either the BB' or EF loop, with such epitope specificity giving rise to the observed biological property of being a "blocking" antibody. Identifying the epitope bound by an antibody is routine in the art, and amounts to further characterization of a reagent disclosed in the prior art. Therefore, a person of ordinary skill in the art would have a reasonable expectation of success in obtaining blocking antibodies that bind the BB' and EF loops since these loops are the domains known to interact with physiological ligands as is discussed in the specification and thus antibodies that bind these loops give rise to the observable

phenomenon of blocking which is disclosed in the prior art (see particularly Example 11 of the instant specification).

Applicant argued as part of the response filed May 9, 2007 that the prior art cannot anticipate because Gorman et al. do not teach that their antibodies inhibit bone resorption. This argument was not persuasive because bone resorption is inhibited by blocking the interaction between OPGbp and OPG. Antibodies that block OPGbp, such as the blocking antibodies of Gorman et al., necessarily inhibit resorption even if this property is not disclosed because the functional property of inhibiting bone resorption is a consequence of the antibody being a blocking antibody.

Applicant also argued as part of the response filed May 9, 2007 that the prior art does not anticipate the claimed invention because Gorman et al. specifically disclose a mouse sequence while the claimed antibodies bind a human sequence. This argument was not found persuasive. First, Gorman et al. explicitly disclose that their invention is not limited to a mouse embodiment (see particularly lines 44-50 of column 9). Second, as has been stated in previous office actions, the mouse and human proteins are 84.1% identical over all amino acid residues, antibodies that crossreact with both human and mouse sequences of the same protein are widely observed and expected in the art, and Gorman et al. explicitly teach that antibodies to mouse 499E9/OPGbp will crossreact with 499E9/OPGbp from other species (see particularly example 4 of Gorman et al.).

Applicant's arguments filed January 25, 2008 have been fully considered but they are not persuasive. Applicant argues that the disclosure of Gorman et al. is not enabled and lacks written description (i.e. possession) of a human OPGbp/499E9 polypeptide and thus the rejection should be withdrawn.

This argument is not persuasive. As the courts stated in *Rasmusson v. SmithKlein Beecham Corp.*, 75 USPQ2d 1297 (CAFC 2005):

> "The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112. In *In re Hafner*, 410 F.2d 1403 (CCPA 1969), the court stated that "a disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is, under the present state of the law, entirely adequate to anticipate a claim to either the product or the

process and, at the same time, entirely inadequate to support the allowance of such a claim." Id. at 1405; see *Schoenwald*, 964 F.2d at 1124; *In re Samour*, 571 F.2d 559, 563-64 (CCPA 1978). The reason is that section 112 "provides that the specification must enable one skilled in the art to 'use' the invention whereas [section] 102 makes no such requirement as to an anticipatory disclosure." *Hafner,* 410 F.2d at 1405; see 1 Donald S. Chisum, Chisum on Patents § 3.04[1][c] (2002); see also In re Cruciferous Sprout Litig., 301 F.3d 1343, 1349-52 (Fed. Cir. 2001) (finding anticipation where applicant sought a patent based on a new use for a previously disclosed method)."

As such, applicant's arguments concerning deficiencies under 35 USC 112 that would disqualify Gorman et al. as prior art are not persuasive. See also *Ex Parte Kubin*, 83 USPQ2d, 1410 (BPAI 2007).

Applicant also argues that an ordinary artisan would not have been able to isolate human OPGbp/499E9 and that antibodies to mouse OPGbp/499E9 would not crossreact with the human polypeptide.

This argument is not persuasive. The phenomenon of crossreactivity is well known in the art, and involves antibodies binding to the same or structurally similar epitopes that are present in distinct biological antigens as is taught by Kuby (Immunology, 1992, page 125). It has been previously established that the mouse and human sequences are quite similar (84.1% identity). Further, the breadth of dependent claims 86 and 87 read on "an epitope on a BB' (or EF) loop" and as such the epitope sequence bound by the antibody is recited as being smaller than the entirety of the BB' or EF loops. It is also known in the art that linear epitopes are about 6 amino acids in length (Antibodies, A Laboratory Manual, 1988, page 76). Given the size of antibody epitopes, the art recognized phenomenon of crossreactivity, the high level of identity between mouse and human sequences, and the breadth of applicant's claims, it appears that antibodies that bind the mouse sequence will also bind the human sequence.

Applicant also argues that the claims recite "specifically bind" and that this means that the claimed antibodies bind only to the human sequence such that crossreactive antibodies do not satisfy the recited claim limitations.

Support for applicant's contention that "specific binding" be limited to only the recited sequence does not appear to be supported by any definition of the term in the specification as filed and is clearly at odds with the phenomenon of crossreactivity

discussed above as defined by Kuby. As such, this argument is also not persuasive. Further, in addition to crossreactive antibodies that bind both the mouse and human sequences, Gorman et al. disclose the full length murine polypeptide and polynucleotide sequences which can be used to isolate OPGbp/499E9 from other animals such as humans, with said human sequences being used to obtain antibodies (see particularly lines 43-50 of column 9 and lines 44-63 of column 16). Note that human (as well as other species) OGPbp/499E9 antigens are disclosed by Gorman et al. as being part of their invention, as are antibodies binding to said antigens (see particularly lines 5-11 of column 15).

The claims stand rejected.

6. Claims 82-92 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (US patent 6,740,522, of record as reference A10 on the 5/14/07 IDS) in view of WO 93/12227 (of record as reference BC on the 3/25/99 IDS) for the reasons of record.

The office action mailed July 25, 2007 states:

> Anderson discloses antibodies that bind RANKL and their methods of use (see entire document, particularly the abstract and claims). He discloses that his antibodies bind RANKL and thereby inhibit binding to RANK (see particularly example 10). Note that the RANKL polypeptide disclosed by Anderson is the osteoprotegerin binding protein (OPGbp) of the instant specification, while RANK is the same polypeptide as osteoprotegerin (OPG). These antibodies are disclosed as inhibiting signaling that occurs through the RANK/OPG receptor (see particularly lines 39-45 of column 3) and are disclosed in therapeutic compositions comprising buffers, cytokines, and diluents (see particularly columns 15 and 16). Structural information concerning the domains within RANKL/OPGbp are also disclosed (see particularly lines 9-35 of column 2 and column 4). These teachings differ from the instant claimed invention in that the antibodies are not disclosed as being human.
>
> The '227 patent discloses methods of making human monoclonal antibodies for use in various treatment methods (see entire document, particularly the abstract). The advantage of using human antibodies for treatment rather than murine monoclonal antibodies is that the human antibodies are less immunogenic than murine antibodies when administered to a patient. This is advantageous because if the administered antibody is immunogenic, the patient's body will make antibodies that neutralize the administered antibody (i.e. the HAMA response) thus eliminating any expected therapeutic benefit (see particularly pages 1 and 2).
>
> Therefore, a person of ordinary skill in the art would have been motivated to make human antibodies that bind the polypeptide disclosed by Anderson because Anderson discloses antibodies that bind RANKL/OPGbp are for therapeutic use and the '227 patent teaches that human antibodies are preferred for therapeutic use because they do not elicit a HAMA response.
>
> It is noted that Anderson does not disclose that his antibodies inhibit osteoclast formation or that his antibodies bind to a particular loop, such as the BB' or EF loops. However, Anderson

does disclose that his antibodies block the binding of RANKL/OPGbp to RANK/OPG and inhibit RANK/OPG signaling. The instant specification discloses that osteoclast formation occurs by the interaction of RANKL/OPGbp with RANK/OPG, and that the binding site on RANKL/OPGbp that allows for binding to RANK/OPG is found in the BB' and EF loops. As such, any antibody that blocks binding and inhibits signaling must be binding the BB' and EF' loops of RANKL/OPGbp.

Applicant's arguments filed January 25, 2008 have been fully considered but they are not persuasive. Applicant argues that the claimed antibodies are not obvious in that they exhibit surprising and unexpected properties. Applicant asserts that these unexpected properties are that antibodies to human OPGbp that inhibit osteoclast formation do not bind murine OPGbp and that therefore they are better for therapy since they are less likely to interact with a molecule unrelated to the target and trigger an adverse event.

This argument is not persuasive. First, binding human but not murine OPGbp is not a limitation of the instantly recited invention. Second, the antigen disclosed by Anderson is human OPGbp, and thus a person of ordinary skill in the art would have made human antibodies to human OPGbp using the same techniques used by applicant. As such arguments concerning crossreactivity between human and mouse sequences do not seem relevant since the person of ordinary skill in the art would have been motivated to make human antibodies to the human antigen for the reasons already of record, i.e. to reduce unwanted adverse immunological events, and thus any other “unexpected” property appears to be an intrinsic property that would necessarily arise as part of making the claimed invention. Also note that if such results were truly “unexpected” a person of ordinary skill in the art would expect these results to apply only to the specific, cloned species of antibodies disclosed in the argued post-filing date references rather than to the generic genus of antibodies that is recited in the instant claims.

The rejection is maintained.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. The office action mailed July 25, 2007 states:

> Claims 82-92 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 45-69 of copending Application No. 10/180,648. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending application 10/180,648 anticipate the instant invention for the reasons of record set forth in the office action mailed May 18, 2005.
>
> This is a provisional obviousness-type double patenting rejection.
>
> Claims 82-92 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20, 22, 23, 25, 27, 29, 31-34, 36-38, 40, 42-50, 52, 59, 60, 62, 64-67, and 76-87 of copending Application No. 10/408,901. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending application 10/408,901 anticipate the genus of antibodies claimed in the instant invention because the copending claims recite antibodies of a specified heavy and light chain sequence. Note that these antibodies are claimed as being fully human (see particularly claims 49, 59, 60, 62, 64-67, and 76-87). Note also that the specification of the copending application discloses on page 70 that the antibodies of the copending application bind human OPGbp.
>
> This is a provisional obviousness-type double patenting rejection.
>
> Claims 82-92 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-20, 27-29, and 40-53 of copending Application No. 09/791,153 in view of WO 93/12227 (of record as reference BC on the 3/25/99 IDS).
>
> The claims of copending application 09/791,153 recite antibodies comprising specific Fab sequences that bind human OPGbp, and indicate that these antibodies comprise human Fc domains (see particularly claims 12 and 13). These claims differ from the instant invention in that they do not teach that the antibodies of a defined sequence (i.e. monoclonal) are human.
>
> The '227 patent teaches that human antibodies offer an advantage over all other antibody type for *in vivo* diagnostic and therapeutic use in that the use of human antibodies reduces anti-therapeutic antibody responses, including HAMA responses (see particularly page 1, lines 27-38). Such responses are generated due to the inherent immunogenicity of non-human immunoglobulins. When non-human antibodies are administered to a human patient, the patient's immune system produces antibodies that neutralize the efficacy of the therapeutic

antibodies, and the resulting antibody complexes can also cause acute toxicity (see particularly page 1, lines 27-38). Human antibodies would not be highly immunogenic in human patients, and as such unwanted anti-antibody responses could be reduced (see particularly page 1, lines 27-38).

Therefore, a person of ordinary skill in the art would have been motivated to make the antibodies recited in the claims of copending application 09/791,153 as human antibodies to gain the advantage of having an antibody of very low immunogenicity that does not elicit unwanted anti-therapeutic antibody responses in the patient such that it can be used in methods of administration to human patients.

This is a provisional obviousness-type double patenting rejection.

Applicant's arguments filed May 9, 2007 have been fully considered but they are not persuasive. Applicant argues that all of the above provisional double patenting rejections are improper because all three copending applications have later effective filing dates than the instant application and therefore the rejections should be removed since a later filed application cannot anticipate an earlier application.

This argument is not persuasive because applicant may always submit a petition for an unintentional delay in a claim for priority and thus the filing dates for the aforementioned copending applications may change. Therefore, the rejections are maintained.

Applicant's arguments filed January 25, 2008 have been fully considered but they are not persuasive. Applicant repeats arguments already of record that since the instant application has the earliest priority date, none of the copending applications qualify as art and thus the rejection should be withdrawn.

This argument is not persuasive for the reasons of already of record. First, removal of double patenting rejections to allow issue of the senior application is only appropriate when no other rejections under other statutes (35 USC 101, 102, 103, or 112) remain. Further, as has been previously stated it is conceivable that petitions to claim earlier priority may be filed in the copending applications such that the earlier priority date would qualify the copending applications as prior art. As such, provisional double patenting rejections serve notice to applicant of the possibility of patentability problems due to overlapping subject matter such that may or may not materialize depending on the prosecution of the instant as well as copending applications.

It is noted that application '153 was abandoned as per the notice mailed 9/7/07 and that a petition to revive an unintentionally abandoned application was received 12/19/07. No decision on the petition has been made at this time, and as such the provisional rejection over the claims of the '153 application are technically withdrawn

since the application is no longer copending. However, if the petition is granted, the provisional rejection over application '153 will be reinstated.

9. No claims are allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Primary Examiner
Art Unit 1644

/Michael Szperka, Ph.D./
Primary Examiner, Art Unit 1644